Treatment of Urinary Tract Infections with a Combination of Amoxicillin and Clavulanic Acid

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A 10-day course of amoxicillin (250 mg)-potassium clavulanate (125 mg) was administered three times daily to 116 female college students with urinary tract infections. All of the bacterial isolates from these patients were susceptible to amoxicillin-potassium clavulanate in vitro; only 81.0% were susceptible to amoxicillin alone. Evaluations at 1 week after completion of this course showed that clinical and bacteriological cures had been achieved in 96.9% of those who completed therapy. Cures were sustained in 85.6% of the patients examined at 4 weeks after the end of therapy. Therapeutic responses were comparable, irrespective of the results of antibody-coated bacteria tests. All strains of *Enterobacteriaceae* isolated from the rectal and urogenital sites at 1 week after therapy were susceptible to amoxicillin-potassium clavulanate. The proportion of fecal *Escherichia coli* resistant to amoxicillin alone increased from 13.3% before therapy to 35.6% at 1 week after therapy. Adverse drug reactions consisted of gastrointestinal symptoms (9.8%) and rashes (4.1%). Sixteen patients (14.2%) developed symptomatic candida vaginitis by 1 week after therapy.

Ampicillin and its analog amoxicillin have been extensively used for the treatment of urinary tract infections (5, 6). The widespread use of these β-lactam antibiotics has been associated with the emergence of resistant strains of various pathogens, resulting in an increased number of therapeutic failures (12, 17, 22). Resistance to these agents is usually mediated by the production of β-lactamases which inactivate these antibiotics (1). Clavulanic acid, a naturally occurring β-lactamase inhibitor, may prevent the inactivation of these β-lactams (8, 21). Combinations of clavulanic acid and amoxicillin are significantly more active both in vitro and in vivo against certain β-lactamase-producing bacteria than is amoxicillin alone (11, 18).

The purposes of this study were: (i) to determine the efficacy and safety of the combination of amoxicillin and potassium clavulanate in the treatment of urinary tract infections; (ii) to attempt to relate therapeutic responses to the results of antibody-coated bacteria tests (25); and (iii) to assess the changes in the carrier state of the resistant urinary pathogens in the rectal, vaginal, and periurethral sites.

MATERIALS AND METHODS

Patient criteria. This study was conducted at the Kidney Clinic of the University of Florida Student Health Service, Gainesville, Fla. All patients were female college students with acute symptomatic urinary tract infections. The major criterion for inclusion was the presence of $\geq 10^5$ colony-forming units (CFU) of the same bacterium per ml in each of three consecutive clean-catch midstream urine specimens. Excluded were pregnant or lactating women and those with impaired renal or liver function, gonorrhea, renal calculus, catheter-induced infection, radiographically proven obstructive uropathy, or a history of allergy to penicillins or cephalosporins. Patients who had received antimicrobial agents during the preceding week were also excluded.

Collection and processing of specimens. After a complete medical history and physical examination, each patient submitted three clean-catch midstream urine specimens for analysis and culture within 24 h before therapy. Urinalyses were performed on uncentrifuged specimens. Antibody-coated bacteria tests were performed as previously described (13, 14, 25).

Vaginal, periurethral, and rectal specimens were collected on Culturette rayon-tipped swabs (Scientific Products, McGaw Park, Ill.) for culture and susceptibility testing before therapy and at 1 week after the end of treatment (14). Vaginal specimens obtained at the above times with a rayon-tipped swab were tested for candida with KOH smear and Nickerson culture (GIBCO Diagnostics, Madison, Wis.).

Bacteriological techniques. Urine specimens were processed and bacterial isolates were identified according to methods described previously (3, 9, 15). Quantitative bacterial counts were performed with a calibrated platinum loop delivering 0.01 ml of urine onto blood agar and MacConkey plates. Antibiotic susceptibility testing of each isolate was performed by the disk diffusion method of Bauer et al. (4) with a 30-

μg amoxicillin-clavulanic acid disk and a 10-μg ampicillin disk. Serotyping for O antigen was performed on *Escherichia coli* isolates (26). Rectal, vaginal, and periurethral specimens were processed for culture and susceptibility testing as previously described (14).

Treatment. Treatment began immediately after the third urine specimen had been obtained, provided that there was at least one organism in each random field examined with a 100× microscopic lens on an unstained, uncentrifuged urine sample. Each patient was given tablets containing 250 mg of amoxicillin trihydrate and 125 mg of potassium clavulanate (AM-CL) (Augmentin; Beecham Laboratories, Bristol, Tenn.) to be taken three times a day for 10 days.

Patients with concurrent vaginal candida were treated simultaneously with vaginal creams containing 2% miconazole nitrate or 1% clotrimazole.

Assessment of therapy. Clinical and bacteriological evaluations were repeated on days 2 or 3 of therapy and on days 2 or 3 and 1, 2, 4, and 8 weeks after completion of therapy. During the first 3 days of therapy, a patient diary was used for recording the clinical course and resolution of the presenting signs and symptoms. Clinical responses were judged to be either complete or partial depending on the disappearance of signs and symptoms by the end of therapy. Complete disappearance was termed a cure; partial disappearance was termed an improvement. An unsatisfactory response, termed a failure, was defined as no appreciable change in signs and symptoms by the end of therapy.

Bacteriological responses were classified as follows: (i) cure, the reduction of the pathogen to $<10^4$ CFU/ml of urine by day 2 of therapy and through 1 week after therapy; (ii) reinfection, the reduction of the initial pathogen to $<10^4$ CFU/ml of urine followed by the emergence of a different organism at a count of $\geq 10^5$ CFU/ml of urine at day 3 after therapy or on subsequent cultures, or the reappearance of the initial pathogen more than 4 weeks after therapy; (iii) relapse, the reduction of the initial pathogen to $<10^4$ CFU/ml of urine by day 2 of therapy and through 2 days after therapy, with the reappearance of the same bacterium at a count of $\geq 10^5$ CFU/ml of urine in subsequent cultures within 4 weeks of the end of therapy; (iv) superinfection, the reduction of the initial urinary pathogen to $<10^4$ CFU/ml of urine by day 2 of therapy, with the emergence of a different organism at $\geq 10^5$ CFU/ml of urine during therapy or within 2 days after therapy; and (v) failure, the persistence or reappearance of the initial urinary pathogen at a count of $\geq 10^5$ CFU/ml of urine during therapy or up to 2 days after therapy or both. All patients with colony counts of $\geq 10^4$ were reassessed with two additional urine cultures.

Evaluation of safety and tolerance. At each clinic visit, patients were questioned for adverse drug reactions such as rashes, nausea, vomiting, or diarrhea. Before and at completion of therapy, the following were measured: serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, creatinine, urea nitrogen, and complete blood cell count. Before therapy and at 1 week after therapy, each patient was tested for occult blood in stool by Hemoccult (Laboratory Diagnostic Corp., Morganville, N.J.).

This study was approved by the Health Center Institutional Review Board of the University of Florida College of Medicine, Gainesville, and a signed statement of informed consent was obtained from each patient.

Statistical analysis. The life table method and the chi-square test were used for analysis of the data (7, 10).

RESULTS

Pretherapy clinical and bacteriological findings. Of 122 patients enrolled in the study, 116 had positive urine cultures ($\geq 10^5$ CFU/ml) and 6 had negative urine cultures ($<10^4$ CFU/ml) before therapy. These six patients presented with dysuria and microscopic bacteriuria, and each received 3 to 10 days of therapy. Although they were excluded from the evaluations of therapeutic efficacy, they were included in the safety assessment.

The mean age of the patients was 22.3 ± 4.2 years, the mean weight was 58.0 ± 1.9 k, and the mean number of symptomatic days before therapy was 2.6 ± 1.9 days. All of the patients had some combination of dysuria, frequency, urgency, and suprapubic pain. A total of 18 patients (15.5%) had costovertebral angle tenderness, 2 (1.7%) had mild fever (37.5 to 38.0°C), 35 (30.2%) had high leukocyte counts ($>10^4$), and 82 (70.7%) had pyuria (≥ 3 leukocytes per high-power field). A total of 71 patients (61.2%) had no history of a urinary tract infection within the preceding 12 months. The remaining 45 (38.8%) had one to two such infections within that period. Candida was isolated from the vagina of 17 patients (13.9%) before therapy.

The distribution of the urinary pathogens by antibody-coated bacteria tests and in vitro susceptibility testing is shown in Table 1. Of the urinary pathogens, all were susceptible to AM-CL; 94 (81.0%) were susceptible to amoxicillin. Of the 22 patients with amoxicillin-resistant urinary pathogens, 5 had received penicillins during the preceding 6 months. A total of 54 (65.9%) of 82 strains of *E. coli* were typable for O antigen. The most common *E. coli* serotypes were O6 (15.9%), O1 (13.4%), O18 (12.4%), and O75 (9.8%).

Test of localization. A total of 34 infections (29.3%) were positive in the antibody-coated bacteria test, and 79 (68.1%) were negative; the test was nonspecific in 3 (2.6%) (25). Signs and symptoms of the upper urinary tract infections (i.e., costovertebral angle tenderness, fever, leukocytosis, and decreased urine-concentrating ability) and of the lower tract infections (i.e., dysuria, urgency, and frequency) did not correlate with the results of this test; that is, the presenting clinical characteristics of the patients were distributed similarly in the positive and negative groups.

Clinical responses. Of the 116 patients, 115 had

TABLE 1. Distribution of urinary pathogens by test of localization and in vitro susceptibility results

Bacterium	No. of patients with antibody-coated bacteria test:				No. of isolates resistant to amoxicillin[a]
	Positive	Negative	Nonspecific	Combined (%)	
Escherichia coli	20	61	1	82 (70.7)	9
Proteus mirabilis	7	3	0	10 (8.6)	0
Staphylococcus saprophyticus	4	3	2	9 (7.7)	0
Klebsiella pneumoniae	3	5	0	8 (6.9)	8
Enterobacter aerogenes	0	5	0	5 (4.3)	4
Citrobacter sp.	0	1	0	1 (0.9)	1
Enterococci	0	1	0	1 (0.9)	0

[a] A total of 19.0% of the isolates were resistant to amoxicillin.

satisfactory clinical reponses after 2 days of therapy. The single clinical failure occurred despite eradication of the bacterial pathogen. A review of patient diaries and subsequent interviews revealed a clinical cure in all of the 104 patients who completed therapy.

Bacteriological response. After the first 2 days of therapy, all 116 patients had negative urine cultures ($<10^4$ CFU/ml of urine). A total of 104 of these patients completed therapy; all had negative urine cultures. Of the remaining 12 patients, 5 did not return, therapy was interrupted in 6 because of adverse reactions, and 1 was removed from the study on day 2 of therapy because of persistence of clinical symptoms. A total of 97 of the 104 patients returned for evaluation at 1 week after the end of treatment; 94 (96.9%) were bacteriologically cured and 3 had become reinfected. A total of 89 (85.6%) were still in the cured category at 4 weeks after the end of therapy. There were 11 reinfections (10.6%) and four relapses (3.8%) (Table 2).

The cumulative rates of recurrence at 1, 2, 4, and 8 weeks after the end of therapy were 3.0, 10.0, 15.0, and 19.0%, respectively (Fig. 1). Reinfections accounted for 15 (78.9%) and relapses accounted for 4 (21.1%) of the 19 recurrences. A total of 10 of the 19 (52.6%) were

inpatients with no history of urinary tract infections in the preceding 12 months. Of the bacterial isolates responsible for the recurrent infections, all were susceptible to AM-CL, and 52.6% were susceptible to amoxicillin.

A total of 29 patients with positive and 72 patients with negative antibody-coated bacteria tests completed therapy. These patients responded similarly to therapy, with no significant differences in the recurrence rates between the two groups (Fig. 1).

Adverse drug reactions. A total of 17 patients (13.9%) had adverse reactions to AM-CL; 12 of these (9.8%) had some combination of nausea, dizziness, vomiting, diarrhea, and abdominal cramps. These symptoms were mild to severe and appeared during the first 8 days of therapy. In two patients, therapy was continued and the symptoms disappeared within 24 h. Five patients tolerated the symptoms and completed the full course of therapy. In five patients, the regimen was discontinued within the first 3 days. All of the untoward symptoms abated spontaneously by 6 days after the end of therapy. Five other patients (4.1%) developed a combination of mild to moderate pruritic or nonpruritic maculopapular, erythematous, or urticarial rashes. These rashes appeared within 2 to 8 days of

TABLE 2. Distribution of patients according to urinary pathogen and bacteriological response by 4 weeks after completion of therapy

Bacterium	No. of patients completing therapy	No. of patients with:			
		Cure[a]	Reinfection[b]	Relapse[c]	Failure
Escherichia coli	73	64	6	3	0
Proteus mirabilis	10	7	3	0	0
Staphylococcus saprophyticus	8	7	1	0	0
Klebsiella pneumoniae	7	5	1	1	0
Enterobacter aerogenes	5	5	0	0	0
Citrobacter sp.	0	0	0	0	0
Enterococci	1	1	0	0	0

[a] Total, 85.6%.
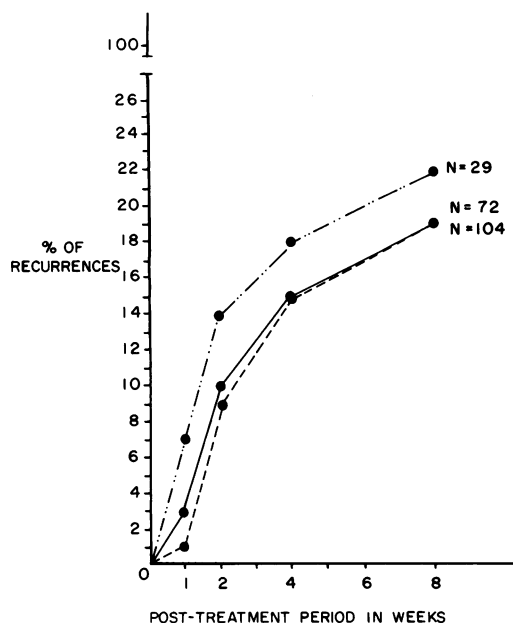[b] Total, 10.6%.
[c] Total, 3.8%.

FIG. 1. Percent cumulative rates of recurrence in antibody-coated bacteria (ACB)-positive (— ·· —), ACB-negative (– – –), and combined (———) groups. N, Number of patients in each group.

therapy. The drug was discontinued after 3 days in one patient and after 8 days in four patients. In three patients, the rashes were mild and vanished within 4 days after the drug was discontinued. Of the remaining two patients, one received antihistamines orally, and the other received antihistamines orally plus epinephrine subcutaneously to alleviate the pruritic rash. A total of 113 patients were screened for vaginal candida within 1 week after therapy. Sixteen patients (14.2%) had candida vaginitis and presented with complaints of vaginal discharge or vulvar irritation or both. Twenty additional pa-

tients (17.7%) had asymptomatic carrier state of vaginal candida.

Blood chemistry values, hemograms, and stool studies. Blood chemistries, hemoglobin, and platelet counts remained normal in all of the patients at the last day of therapy. Of 110 patients with initially normal values, alanine aminotransferase increased to 46 to 95 in 4 (3.6%) (normal = 7 to 40), leukocyte counts dropped to 3,900 to 4,600 in 6 (5.5%) (normal = 4,800 to 10,800), and eosinophil counts rose to 5 to 8% in 15 (13.6%) (normal ≤ 0 to 4%). These changes were transient and returned to normal within 1 to 2 weeks after completion of therapy. Two of the patients with decreased leukocyte counts and two with increased eosinophil counts were among those who had adverse drug reactions.

At 1 week after therapy, stool was positive for occult blood in three patients. One of these had hemorrhoids and constipation; another had candida vaginitis associated with perianal dermititis and superficial fissures. No obvious cause was found in the third patient, but her test was negative after 1 week.

Changes in the carrier state of periurethral, vaginal, and fecal flora. Specimens for culture and susceptibility testing were obtained from periurethral, vaginal, and rectal sites of 96 patients before and at 1 week after therapy. All of the Enterobacteriaceae isolated from these sites were susceptible to AM-CL before and at 1 week after the end of therapy. The prevalence of fecal E. coli resistant to amoxicillin increased from 13.3% before therapy to 35.6% at 1 week after the end of treatment (Table 3).

The number of carriers of amoxicillin-resistant Enterobacteriaceae in at least one of the three culture sites increased from 39 (41%) before therapy to 63 (66%) at 1 week after therapy. A total of 19 patients (20%) had a carrier state of amoxicillin-resistant Enterobacteriaceae in at

TABLE 3. Distribution of bacterial isolates according to culture site in 96 patients before and after completion of therapy with AM-CL

Bacterium	No. of isolates (no. resistant to amoxicillin) from:					
	Periurethra		Vagina		Rectum	
	Before	After	Before	After	Before	After
Escherichia coli	61 (10)	48 (13)	54 (10)	42 (12)	120 (16)	118 (42)
Proteus mirabilis	5	4	3	3 (1)	2	4 (1)
Staphylococcus saprophyticus	4 (1)	1 (1)	1	1 (1)	0	0
Klebsiella pneumoniae	8 (6)	16 (13)	12 (10)	19 (16)	11 (8)	13 (8)
Enterobacter sp.	4 (2)	6 (3)	4 (1)	5 (4)	6 (3)	5 (4)
Other	7 (1)	12 (1)	6 (1)	13 (1)	8 (2)	5 (1)
No. of patients with no pathogenic isolates	20	37	38	40	0	1

least one of the culture sites both before and at 1 week after therapy.

DISCUSSION

There have been only two previously reported clinical trials with AM-CL combinations. Goldstein et al. have reported that a single oral dose of amoxicillin (500 mg) and clavulanic acid (100 mg) cleared amoxicillin-resistant urinary pathogens in five of six patients (11). Ball et al. have reported cure rates of 30% for amoxicillin-resistant and 70% for amoxicillin-susceptible urinary tract infections in 20 patients who received amoxicillin (250 mg) and sodium clavulanate (125 mg) three times daily for 7 days (2). They attributed the poor therapeutic response to the decreased renal excretion of the antibiotic in their patients, who were described as either being elderly or having complicated, recurrent urinary tract infections. In the present study, the therapeutic results were highly acceptable, and AM-CL was equally effective for urinary tract infections caused by either amoxicillin-susceptible or amoxicillin-resistant organisms.

Over 90% of amoxicillin administered orally is absorbed from the small intestine (MacLeod et al., Clin. Res. 21:1018, 1973). Intestinal absorption of clavulanic acid is of a similar order (2). Thus, the lack of suppression of the fecal *E. coli* and other *Enterobacteriaceae* by AM-CL may be because of a low residue of the drug in the bowel. Shaw and Datta have reported that ampicillin and, to a lesser extent, amoxicillin cause the appearance of resistant fecal *E. coli* (24). The emergence of amoxicillin-resistant *E. coli* and other *Enterobacteriaceae* after therapy with AM-CL has not been reported. However, low concentrations of either ampicillin or amoxicillin may induce the bacteria to produce β-lactamases in vitro and render the organism resistant (19). Clavulanic acid does not possess this characteristic, and it inactivates these enzymes (8, 21). The bacterial strains responsible for the recurrences were all susceptible to AM-CL, but 47.4% of them were resistant to amoxicillin. This correlated with the increased prevalence of the amoxicillin-resistant organisms isolated from the fecal and urogenital flora after therapy.

Adverse drug reactions in our patients consisted of gastrointestinal symptoms (9.8%) and rashes (4.1%). Increases in the serum transaminases and changes in the hemograms were minimal and transient. However, the incidences of symptomatic candida vaginitis (14.2%) and asymptomatic carrier state of vaginal candida (17.7%) were high. In contrast, Ball et al. have reported excellent tolerance of amoxicillin (250 mg) and sodium clavulanate (125 mg) in 20 elderly patients. A total of 8 of 20 other patients (40%) who received higher doses of amoxicillin

(500 mg) and sodium clavulanate (250 mg) had nausea and vomiting. One patient had a rash, and another had candida vaginitis (2). Adverse reactions similar to those described for AM-CL have been reported with amoxicillin alone (6, 20, 23, 27). Neringer and Stromberg have reported gastrointestinal symptoms (21.3%), vulvovaginal irritations (4.5%), and rashes (10.5%) with amoxicillin (20). Wise and Neu have reported gastrointestinal symptoms (3.2%), rashes (1.8%), and candidiasis (0.4%) in 1,181 patients of both sexes and various ages after different dosages of amoxicillin (27). We have observed mild to moderate diarrhea (2.7%), rashes (2.7%) (23), and candida vaginitis (11.4%) in 35 female college students who received 250 mg of amoxicillin three times daily for 10 days. However, a controlled randomized study of amoxicillin and AM-CL is required to compare the efficacy and safety of these drugs more precisely.

There was a lack of correlation of the antibody-coated bacteria test with the presenting clinical signs and symptoms of the upper and lower tract infections. Patients with a positive or a negative test had similar responses to therapy. Patients with a positive test did not show a propensity for recurrence rates higher than those of patients with a negative test (13, 14, 23). We feel that further studies are required to clarify the clinical significance of this test.

Urinary tract infections in young women are most often uncomplicated and respond well to the commonly used antibacterial agents, provided that the bacteria are susceptible (16). Therefore, amoxicillin would have been as effective as AM-CL in patients whose urinary tract infections were caused by amoxicillin-susceptible organisms. However, considering the high incidence of amoxicillin-resistant urinary pathogens and the fact that treatment of acute urinary tract infections is usually started before the availability of the bacterial susceptibility results, the combination of amoxicillin and a β-lactamase inhibitor may be preferable to amoxicillin alone in initiating antibacterial therapy. Depending on the bacterial susceptibility results, therapy may be completed either with AM-CL or with amoxicillin alone.

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